Applying Green Chemistry to the Photochemical Route to Artemisinin

Zacharias Amara,[1] Jessica F. B. Bellamy,[1] Raphael Horvath,[1] Samuel J. Miller,[1] Andrew Beeby,[2] Andreas Burgard,[3] Kai Rossen,*[3] Martyn Poliakoff*[1] and Michael W. George*[1]

[1] School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK.

[2] Department of Chemistry, University of Durham, South Rd, Durham DH1 3LE, UK.

[3] Sanofi-Aventis Deutschland GMBH, C&BD Frankfurt Chemistry, Process Research, Industriepark Hoechst. D-65926 Frankfurt am Main, Germany.

* Corresponding authors: e mail Kai.Rossen@sanofi.com, Martyn.Poliakoff@nottingham.ac.uk, Mike.George@nottingham.ac.uk

Artemisinin is an important antimalarial drug but, currently, the environmental and economic costs of its semi-synthetic production are relatively high. Most of these costs originate in the final chemical steps which follow a complex acid- and photo-catalysed route with oxygenation by both singlet and triplet oxygen. We demonstrate that applying the principles of green chemistry can lead to innovative strategies which avoid many of the problems in current photochemical processes. The first strategy combines the use of liquid CO_2 as solvent and a dual-function solid acid/photocatalyst. The second is an ambient temperature reaction in aqueous mixtures of organic solvents; the only inputs are dihydroartemisinic acid, O_2, and light — the output is pure, crystalline artemisinin. Everything else — solvents, photocatalyst and aqueous acid — can be recycled. Some aspects developed here through green chemistry are likely to have wider application in photochemistry and other reactions.

The principles of green chemistry[1,2] are a checklist of metrics for judging the environmental cost and efficiency of a given chemical reaction or process. These principles include minimization of waste, avoidance of toxic solvents and reagents, elimination of unnecessary steps and minimization of energy usage. Their application has been particularly effective in pharmaceutical manufacture, not least because those processes often involve many steps, each of which may involve toxic compounds and generate waste. For example, in the case of Viagra, application of these principles has led to a huge reduction in solvent usage.[3] Green chemistry principles often lead to simplified and cost effective strategies which, as we demonstrate here, can open up new processing opportunities.

Minimizing the financial and environmental costs of manufacturing artemisinin (**1**) is a major goal for supplying this antimalarial drug at a price that would permit its even wider use in economically developing parts of the world.[4,5] The current supply of **1** obtained by extraction from *Artemisia annua* does not always meet demand. Therefore, supplementing this with a semi-synthetic manufacturing process from more abundant biosynthetic precursors is a promising way forward.[6] Photochemical generation of singlet oxygen, $^1O_2$, is a key step in the only commercially viable route for the semi-synthetic production of **1**. It begins with a biosynthetic step,[7] namely the use of genetically modified yeast to convert glucose to artemisinic acid, **2**, which is then hydrogenated diastereoselectively to **3** (Fig. 1).[8-10] With the carbon skeleton already assembled, the final conversion of **3** to **1** formally requires the introduction of two O_2 molecules. In this context, photochemically generated $^1O_2$ is attractive from a green chemistry point of view because (a) both of the oxygen atoms are incorporated

into the product, avoiding waste and (b) photochemical energy is delivered selectively unlike thermal reactions, which require the heating of the entire reaction mixture.

In the industrial process currently implemented at Sanofi, the oxygenation is preceded by an additional step, the esterification of **3** to a mixed anhydride.[10] However, the direct Schenck ene oxidation of **3** with photochemically generated $^1O_2$ is also possible, as first described by Acton and Roth[11,12] and more recently by Seeberger and coworkers in an elegant continuous process.[13,14] This can lead several possible regioisomeric hydroperoxides, only one of which, **4**, can be transformed into **1** (see ESI, Scheme S1). The only other isomer generated in any reasonable quantity is **5** and the ratio of **4**:**5** has been shown to be highly temperature dependent in a range of solvents,[10,13-15] with low temperatures favoring the formation of **4**. The resulting hydroperoxide **4** is then converted to **1** in an acid-catalyzed rearrangement followed by a second oxygenation, a sequence studied in some detail by Brown and co-workers.[15,16]

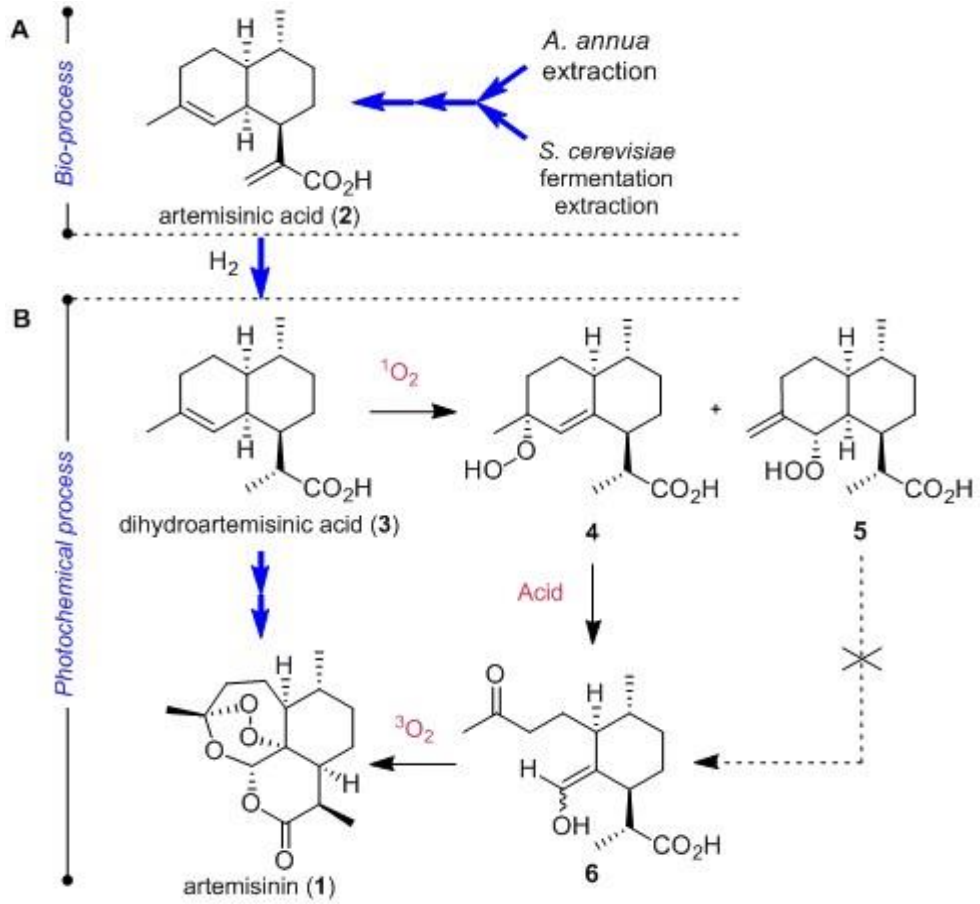

Fig. 1. Semi-synthetic production of the potent anti-malarial artemisinin, **1.** (**A**) Initial production of artemisinic acid (**2**) either by extraction from *Artemisia annua* or by a fed-batch fermentation processes (*Saccharomyces cerevisiae*). (**B**) Chemical conversion of **2** to **1** by hydrogenation to **3** followed by photo- and acid-catalysis. **5** is the predominant unwanted hydroperoxide, formed during reaction of **3** with $^1O_2$. The current Sanofi process adds an extra activation step to form the ester of **3** (mixed anhydride) rather than the free acid.[10] Hydroperoxide **4** is converted through an acid-catalyzed ring opening process into enol **6** (**6** has been observed under oxygen free conditions). This reactive intermediate is then finally oxidized into **1**, a step which requires heating to room temperature and longer reaction times.

The current industrial process and all of the published work mimic the biosynthetic route to **1** in a genuinely atom economical way. Most variations of this route give between 50% and

60% yield of **1** after optimization (55% for the industrial process) which appears an inherent limitation of the chemistry rather than a function of the particular process. Nevertheless, these approaches fail to tackle a number of key green chemistry issues. These begin with the use chlorinated solvents such as dichloromethane (DCM) for the $^1O_2$ reaction; the use of the relatively toxic acid, trifluoroacetic acid (TFA); the need to carry out the photo-oxidation at low temperature (typically -20^{o}C) to increase selectivity towards **4**;[13-15] and the ultimate purification of **1**, involving multiple washings to remove the acid, the loss of photosensitizer and solvent exchange to allow crystallization.[10] In addition, all of these processes generate **1** in the presence of free acid which is concerning because **1** is not stable under acidic conditions[17] and this could ultimately reduce productivity.

Here we outline two separate and different strategies, based on principles of green chemistry, which circumvent most of these problems. These strategies are (i) the use of liquid CO_2 as the reaction solvent, using a potentially recyclable heterogeneous photosensitizer/acid system as shown in Fig 2 and (ii) the use of recyclable aqueous mixtures containing water soluble acid- and photo-catalysts, see Fig 3. Below, we describe these approaches in more detail and then compare them in terms of "green metrics" and their possible impact on the environmental cost of production of **1**.

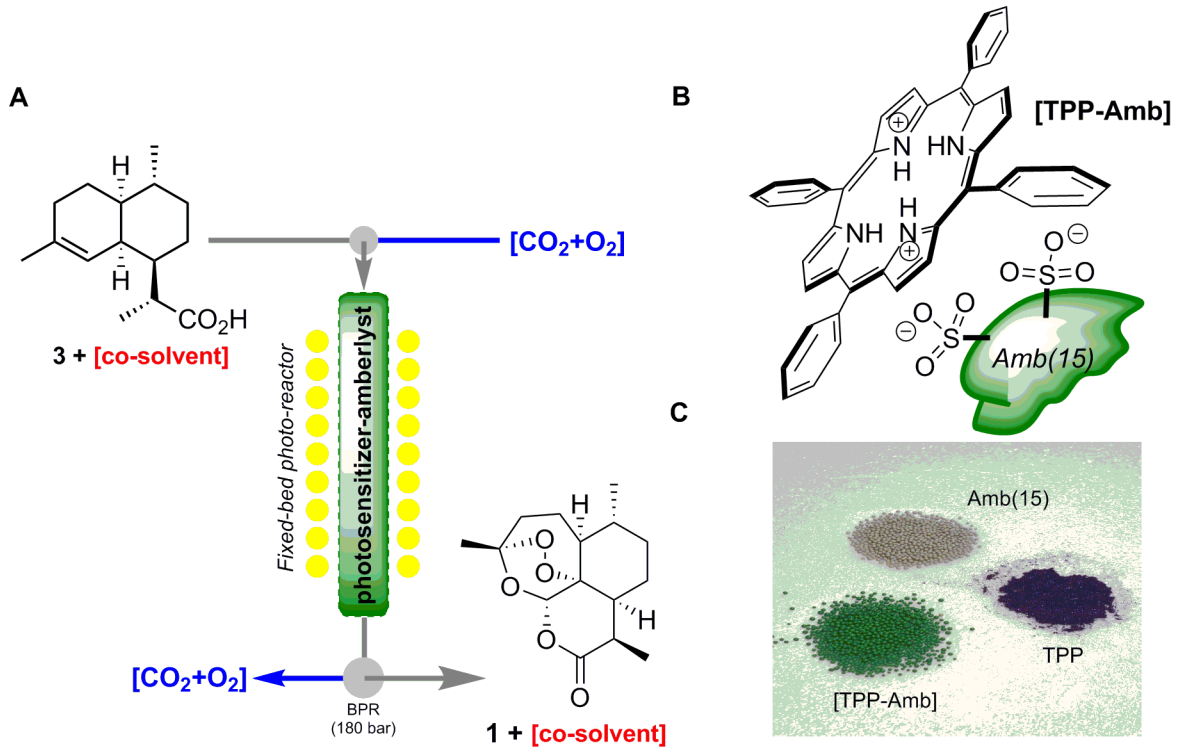

Fig. 2. Our first strategy, the one-pot semi-synthesis of artemisinin in *liquid* CO_2 with a dual function heterogeneous catalyst. (**A**) Schematic of the continuous flow reactor; it consists of a transparent sapphire tube containing the immobilized photocatalyst, surrounded by a concentric transparent cooling jacket and three banks of high power white light emitting diodes (LEDs, see the ESI for a fuller description). As **3** is a solid, a co-solvent is required to enable pumping into the reactor. (**B**) Schematic of the catalyst, consisting of porphyrin photosensitizer bound to Amberlyst-15. While similar work has been carried out to immobilize porphyrins and phthalocyanins by a number of groups,[27-30] using covalent linkages,[29,30] electrostatics,[28] and embedding,[28] we believe that in this case it is the basicity of the porphyrin that enables anchoring through di-protonation of the porphyrin core.[31] (**C**) Photograph showing the difference in color between the free and the supported porphyrins and Amberlyst 15.

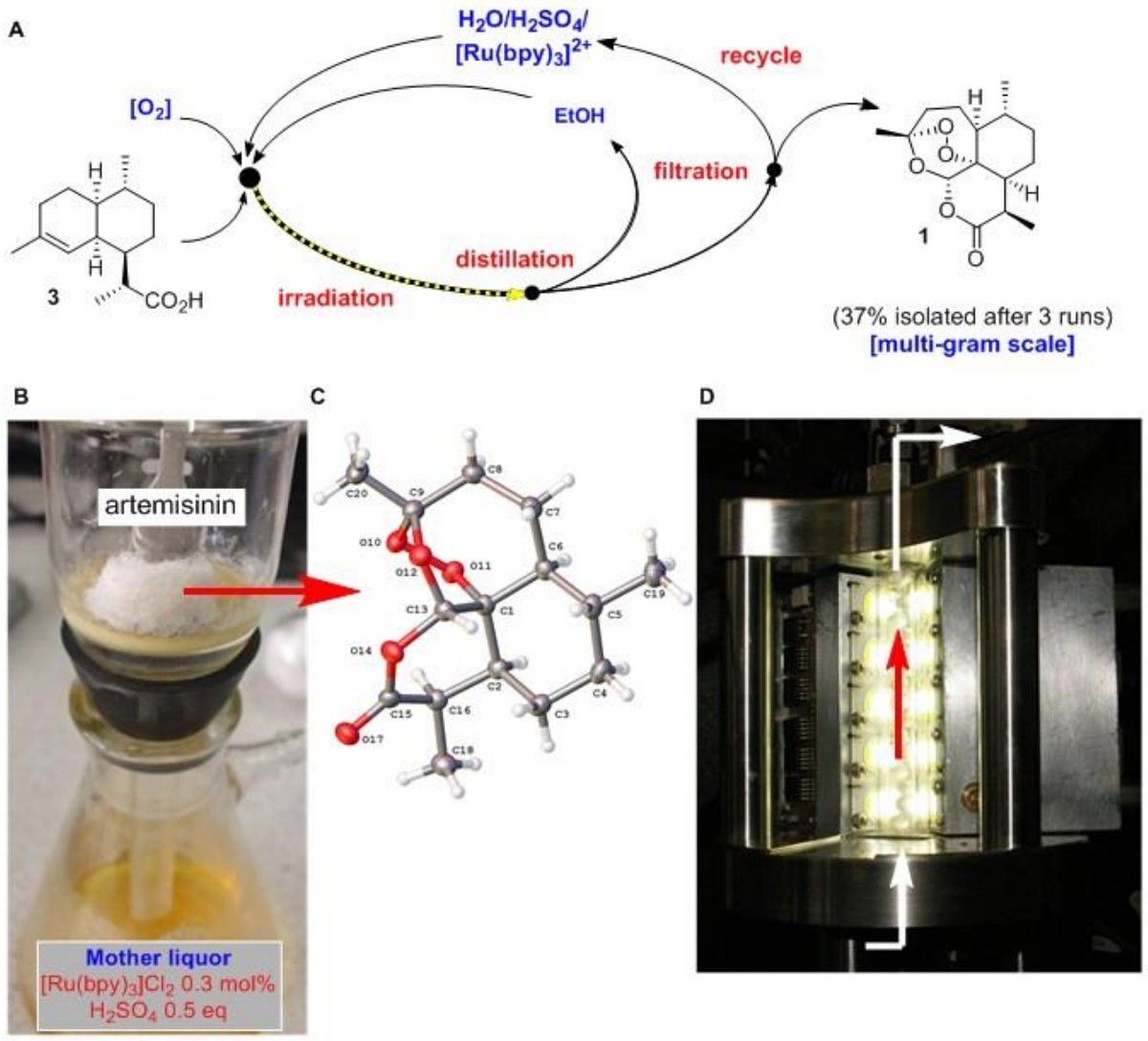

Fig. 3: Our second strategy, photocatalytic oxygenation of **3** dissolved in EtOH + H_2O, (**A**) Schematic of the non-optimized process illustrating how **1** can be recovered from the solution by partial evaporation of the EtOH to reduce the solubility of **1** in the aqueous solvent. (**B**) Photograph taken at the filtration stage, showing crystals of **1**. (**C**) Single crystal X-ray structure obtained from a crystal removed directly from the crude solid without any further re-crystallization. (**D**) Photograph of the high pressure photo-reactor modified for upward flow of aqueous mixtures, showing the sapphire tube filled with glass balls and surrounded by LEDs.

Strategy 1: Dual-functional heterogeneous photocatalysis in liquid CO_2

CO_2 is an attractive solvent for greener chemistry because it is cheap, renewable and non-toxic. For reactions of $^1O_2$, it has the benefit of being non-flammable and the lifetime of $^1O_2$ is relatively long,[18] which is of key concern when selecting a suitable solvent for photo-oxidation reactions. In addition, supercritical CO_2 ($scCO_2$) has been shown to be a useful solvent for reactions involving permanent gases (e.g. H_2, CO or O_2) as they are completely miscible with $scCO_2$.[19-21] Our group recently demonstrated that the reactions of $^1O_2$ can be carried out efficiently in a continuous flow reactor in $scCO_2$ with either homogeneous or immobilized porphyrin photocatalysts.[22-26] We have now applied this approach to the reaction of $^1O_2$ with **3** at low temperature, taking CO_2 into the *liquid* phase, with an added advantage for scale-up since the vapour pressure of liquid CO_2 is much lower than for $scCO_2$, thereby reducing the pressure requirements for future reactors. Until now, *liquid* CO_2 has

rarely been used as a solvent because most reactions carried out in CO_2 have been *thermally* initiated which almost immediately raises CO_2 above its critical temperature, 31 ^oC.

As shown in Fig 2, we have used an immobilized porphyrin in order to remove the need to separate the photocatalyst from the product. In the past, porphyrin immobilization has most often been carried out through covalent bonding but this involves multiple low yielding steps to modify the photocatalyst and tedious work up procedures.[23] We have developed a simple method that enables straightforward anchoring of *meso*-tetraphenylporphyrin (TPP) or *meso*-tetrakis(pentafluorophenyl)porphyrin (TPFPP), both of which are commercially available, porphyrins onto the sulfonated cross-linked polystyrene ion-exchange resin, Amberlyst-15 (Amb), see Fig. 2 and ESI. This gives a *dual catalyst* with both the Brønsted acidic and photo-catalytic functions needed to convert **3** to **1**.

A number of different conditions were investigated with TPP-Amb which appears to be the more robust bifunctional system with negligible leaching (entry 3 and ESI Table S1); these results are comparable to the use of a *homogeneous* system, using TPFPP and *2*-mesitylene sulfonic acid, both of which are soluble in liquid and $scCO_2$ (see ESI). Full conversion was achieved after four passes at 0.12 $mL.min^{-1}$ (entry 3). Interestingly, doubling the length of the photoreactor resulted in near 100% conversion of **3** in a single pass at the same flow rate (entry 4). The conditions were not fully optimized but nevertheless yields ca. 50% were obtained (entries 3 & 4), comparable to published routes.[9,13] Most yields were measured directly from NMR of the product solution but some samples of **1** were isolated and more fully characterized by a variety of techniques including NMR, melting point and optical rotation; the data are in excellent agreement with those recorded from an authentic sample of **1** from the commercial process (see ESI).

As with previously reported batch reactions,[15] it was found that acid must be present at the photo-oxidation step to minimise the formation of by-products arising from elimination of H_2O_2 from **4**. The bifunctional nature of the TPP-Amb/CO_2 system therefore has the advantage that **4** is no longer accumulated in the reaction medium and undergoes Hock rearrangement more selectively. In addition, combining the use of CO_2 and these bifunctional heterogeneous catalysts enables **1** to be obtained directly at the outlet of the photoreactor with 50% yield. This contrasts with previous studies, where **1** was only obtained after further heating of the solution under an atmosphere of O_2[10,13,14] and there remains substantial scope for further improvement of these parameters: a key factor being the concentration of O_2, where we have limited ourselves to 2 mol%.

Table 1. Continuous `one-pot' synthesis of artemisinin from **3** using CO_2 as the reaction solvent.[a]

Entry	Co-Solvent	Catalyst	CO_2 (mL min^{-1})	**3**[b] (mL min^{-1})	Pass	Conv.[c] (%)	Yield[c] (%)
1	EtOAc	TPFPP-Amb[d]	0.53	0.05[e]	1	92	50
2	Toluene	TPFPP-Amb[d]	0.53	0.12	1	50	33
3	Toluene	TPP-Amb	0.53	0.12	1	63	25
					2	82	39
					3	93	48
					4	98	51[g]
4	Toluene[f]	TPP-Amb	0.53	0.12	1	>98	48[g]

[a] Operation at 5 °C, 18 MPa, 2 mol.% O_2. [b] Concentration of **3** is 0.5M (see ESI) [c] Reaction conversion and yield were calculated based on the integration of the relevant peaks in the ^{1}H-NMR spectrum according to internal standard (mesitylene); some material is lost via formation of **5** in the initial Schenck ene reaction, and more is lost via formation of oligomers, see Fig. 5; [d] Some leaching of TPFPP from Amberlyst-15 support was observed. [e]This experiment used a higher CO_2:**3** ratio to avoid system blockage. [f] Using a double-length reactor with double residence time in photoreactor, see ESI for details. All reactions were run at a reactor temperature of **5** °C (corresponding to a total residence time of *ca.* 10 min) to increase the formation of **4** over its regioisomers. [g] Although this strategy was not fully optimized, these conditions gave the highest yields and are those that have been used in the calculation of the E-factors in Table 3 and ESI.

Strategy 2: Reactions in aqueous mixtures of organic solvents

This strategy arose from control experiments in conventional solvents carried out in parallel to our work on liquid CO_2. When photo-oxidation of **3** was carried out as a batch reaction in conventional glassware, in carefully dried tetrahydrofuran (THF), surprisingly not a trace of **1** was obtained**,** just a complex mixture of byproducts. By contrast, with *wet, non-distilled* THF, the yields of **1** were relatively high (>60%), indicating that the reaction requires a minimum amount of water to proceed. This suggested that the reaction might perhaps be run in aqueous solvent mixtures, with corresponding benefits in the context of green chemistry. Even though reactions involving photochemically generated $^1O_2$ in the presence of H_2O have occasionally been reported,[32-34] the use of aqueous solutions in preparative photochemistry has been largely overlooked, probably because water and other protic solvents are excellent quenchers which reduce the lifetime of $^1O_2$.[35,36]

With these facts in mind, the effect of the presence of **3** on the emission lifetimes of $^1O_2$ was investigated in DCM, pure EtOH and a 1:1 (v/v) mixture of EtOH + H_2O. The results are summarized in Fig. 4. Mono-exponential decays provided good fits for all acquired traces. Plotting of reciprocal lifetimes versus the concentration of **3** yielded linear relationships for all three solvent systems, giving values for the photo-physical quenching constant (k_q) of 4.1 x 10^5, 1.6 x 10^5, and 9.6 x 10^5 $Lmol^{-1}s^{-1}$ for DCM, EtOH, and EtOH + H_2O, respectively. Surprisingly the addition of H_2O to EtOH *increases* the value of k_q — that is the rate at which $^1O_2$ reacts with **3**. This effect contrasts with the efficient quenching of $^1O_2$ in H_2O. Clearly, the addition of H_2O is less detrimental to the photo-oxidation reaction than one might anticipate by solely considering the reduced excited state lifetimes of $^1O_2$ in an aqueous system.

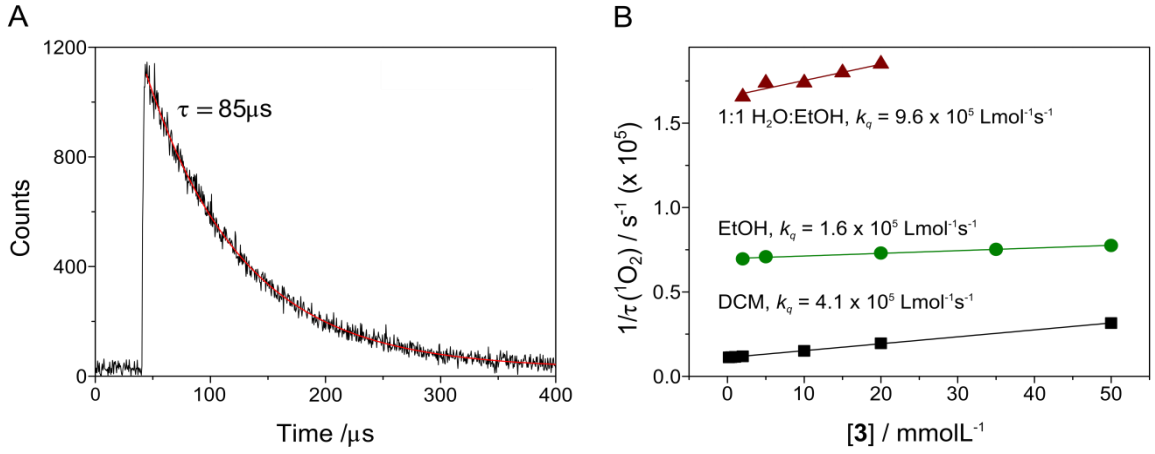

Fig. 4. $^1O_2$ emission following photo-excitation with a 355 nm pulse. (**A**) Emission trace for [**3**] = 5 $mmolL^{-1}$, in DCM, data fitted with a single exponential. (**B**) Stern-Volmer plots showing the quenching of $^1O_2$ emission by **3** in different solvent systems. The increased value of k_q indicates that $^1O_2$ can react with **3** at these concentrations, even in the presence of H_2O.

Conducting the photo-oxidation of **3** with O_2 (0.1 MPa) in mixtures of THF or EtOH with H_2O and water-soluble photosensitizers confirmed this finding; indeed, the yields of **1** were similar to those obtained in DCM and in one case higher (see Table 2, entry 2). In addition, the presence of water meant that TFA could be replaced by H_3PO_4 (entry 4), or H_2SO_4 (entries 7 - 10) which is insoluble in DCM and has been reported to promote dehydration of intermediate **6**.[14] Surprisingly, unlike many of the solvent systems previously studied,[13] the aqueous mixtures gave a high ratio of **4:5** that was essentially unchanged between – 30 ^oC

and + 30 °C, thereby eliminating the need for energy-hungry refrigeration. The reaction also gave good yields of **1** with two different water-soluble ionic photosensitizers, $[Ru(bpy)_3]^{2+}$ or TMPyP (see Table 2).

Table 2. Solvent, photosensitizer and acid conditions screening.[a]

Entry	Solvent	Ratio	[2] mol.L^{-1}	Photosensitizer	T(°C)	Acid	Eq.	Yield[b] (%)
1	DCM		2.1×10^{-2}	TPP	10°C	TFA	0.5	54
2	THF:H_2O	60:40	5.3×10^{-2}	$[Ru(bpy)_3]Cl_2$	10°C	TFA	0.5	66[c]
3	THF:H_2O	60:40	5.3×10^{-2}	$[Ru(bpy)_3]Cl_2$	30°C	TFA	0.5	59
4	THF:H_2O	60:40	5.3×10^{-2}	$[Ru(bpy)_3]Cl_2$	0°C	H_3PO_4	0.5	52
5	THF:EtOH:H_2O	5:75:20	2.1×10^{-2}	$[Ru(bpy)_3]Cl_2$	10°C	TFA	0.5	62
6	EtOH:H_2O	50:50	2.1×10^{-2}	$[Ru(bpy)_3]Cl_2$	10°C	TFA	1.0	43
7	EtOH:H_2O	50:50	2.1×10^{-2}	$[Ru(bpy)_3]Cl_2$	10°C	H_2SO_4	1.0	40
8[d]	EtOH:H_2O	80:20	1.7×10^{-1}	$[Ru(bpy)_3]Cl_2$	0°C	H_2SO_4	0.5	50
9	EtOH:H_2O	80:20	5.3×10^{-2}	$[Ru(bpy)_3]Cl_2$	30°C	H_2SO_4	0.5	39
10	EtOH:H_2O	60:40	2.1×10^{-2}	TMPyP[e]	10°C	H_2SO_4	0.5	53
11	^{i}PrOH:H_2O	60:40	5.3×10^{-2}	$[Ru(bpy)_3]Cl_2$	0°C	TFA	0.5	59

[a] Unless otherwise stated, the reactions were conducted on 250 mg scale using 1 mg of photosensitizer in a solvent volume of 20 mL. Photo-irradiation was carried out for 5 hours. [b] The yield was measured by ^{1}H NMR using mesitylene as an internal standard, added after work up. In each experiments, conversion was higher than 98%. [c] This is the highyest yield opbtained so far and was used in the calculation of E-factors in Table 3, entry 8. [d] This reaction was conducted on 6 g scale using 10 mg of photosensitizer in 150 mL solvent volume. Photo-irradiation was carried out for 8 hours. [e] 5,10,15,20-tetrakis(*N*-methylpyridinium-4-yl)porphyrin tetra(*p*-toluenesulfonate).

The overall yield of **1** was found to be higher in solutions containing THF (up to 66% yield, Table 2 entries 3-5) than in EtOH/H_2O (entries 6-10), even if only small quantities of THF were present (entry 5). THF, which is not itself a nucleophile, may well have a "protective effect" against acid-catalysed degradation, see Fig. 5.

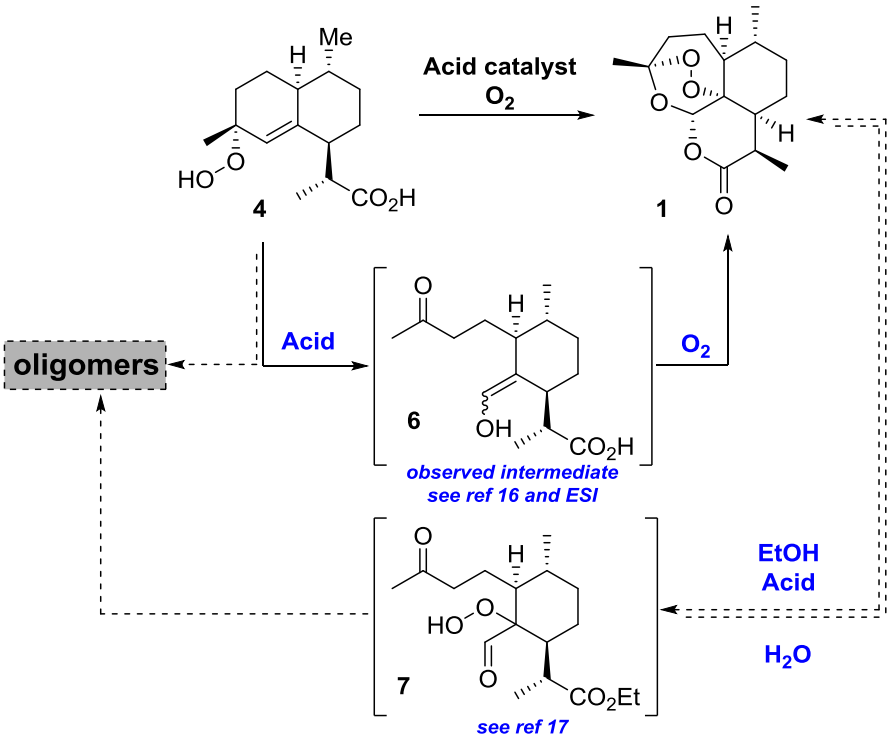

Fig. 5. Proposed acid catalyzed degradation pathways, which occur during or after the reaction and suggest why H_2O reduces the extent of degradation. Evidence for these pathways includes polar oligomeric materials (*ca.* 30-40% yield), isolated by column chromatography of the mother liquors left after crystallization of **1**; these side products were amenable to MALDI analysis (see ESI), and their presence may explain the observed yield limitations for **1**.

It seems likely that the presence of H_2O also reduces the extent of degradation by reversing the equilibrium and inhibiting radical polymerization (see Fig. 5). H_2O does, however, reduce the rate of conversion of **6** to **1** and the reaction has to be kept agitated at room temperature and under an oxygen atmosphere for an additional period of time. We therefore attempted to deconstruct the cascade leading to **1** and found that **6** is formed with *ca.* 50% selectivity, determined by NMR using biphenyl as an internal standard (see ESI, Fig. S10). It is perhaps not surprising that the selectivity drops at that stage considering that the reaction intermediates leading to **6** are highly prone to undergoing intermolecular aldol condensation, dehydration or radical side reactions that can lead to the formation of complex oligomers, as shown by MALDI analysis (see ESI).

Given the recognized advantages of continuous processing, a flow system was implemented using EtOH/H_2O and THF/H_2O as the reaction solvents and H_2SO_4 as the acid. The reactions were carried out in the same tubular photoreactor as used with CO_2, but modified for upflow and filled with 6 mm diameter glass beads to promote mixing and reduce the optical pathlength to prevent inner filter effects, see Fig. 3D. The glass beads reduced the free volume of the reactor. Therefore, in order to maintain reasonable productivity, the conversion of **3** to **4** in THF/H_2O and EtOH/H_2O (80:20) was accelerated by using higher pressures of O_2; at a pressure of 1 MPa, the photo-conversion is largely completed at a residence time of ca. 20 min**,** (see ESI for experimental details) but as before, the final formation of **1** takes considerably longer. This is less of a problem then it might appear because it occurs in the presence of air in the product collection flask.

Perhaps, the most striking aspect of using H_2O as a reaction solvent is seen during product work up because partial evaporation of EtOH or THF from the aqueous mixtures results in the spontaneous crystallization of pure **1**, see Fig. 3B/C and ESI. At the same time, the H_2O-soluble photosensitizer and the acid remain in solution, available for continued use. Therefore, we have demonstrated the recycling of not only the aqueous solution of photosensitizer and acid catalyst but also of the evaporated EtOH for three cycles with no loss in yield of **1**. As shown in Fig. 3A, the result is a simple process where the only inputs are **3**, light, O_2 and heat; the sole output is **1**.

How do these strategies compare?

Both strategies presented above involve flow chemistry. Therefore the amount of product obtained depends on how long the reactors are run. **1** has relatively low solubility in our solvent systems [toluene + CO_2] (strategy 1) and [EtOH + H_2O] (strategy 2) and the solutions are more dilute than in published work.[10,13] However, this dilution is compensated by the efficiency of our reactors so that the space time yields in strategies 1 & 2 are 2.5 g/mL/day and 3.4 g/mL/day respectively, comparable to literature data for producing **1** by flow chemistry.[13] The reaction in aqueous solvent (strategy 2) can be operated indefinitely as reactants and catalysts are in homogeneous solution. By contrast, with liquid CO_2 (strategy 1) there is a heterogeneous catalyst and the running time will eventually be limited by bleaching of the supported porphyrin. The main differences from the literature lie in the overall processing time, temperatures and greatly reduced workup necessary to recover the product. Strategy 1 delivers **1** directly at the outflow while the aqueous chemistry in strategy 2 requires additional time for the formation of **1**. On the other hand, the aqueous strategy 2 can be used in either flow or batch processes and could easily be implemented on the existing industrial-scale plant;[10] strategy 1 would require new higher pressure equipment; however, it has already been demonstrated[21] that lab-scale tubular reactors for thermal chemistry can be

successfully scaled out into parallel reactors for commercial scale production while still only using the same number of pumps and compressors as in the laboratory.

But how green are these strategies? Qualitatively, one can rate them using the Twelve Principles.[1] Although some of our experiments used TFA, both strategies can operate without TFA, thereby avoiding toxic reagents (Principle 3). Unlike the literature[13] or industrial[10] processes, neither strategy requires a separate solvent for workup, thereby minimizing solvent usage (Principle 5). The use of CO_2 in strategy 1 does contravene Principle 6, namely that reactions should be run as close as possible to ambient temperature and pressure to minimize consumption of energy. However, both strategies run at higher temperatures than other processes and cooling is energy intensive; indeed, one paper by Seeberger's group reported that cooling their photoreactor consumed 70% of the total energy budget.[13] Apart from toluene, all of the solvents used here (i.e. THF, EtOAc, EtOH, *i*PrOH, H_2O and CO_2) are environmentally benign[37] and preferable to the halogenated solvents currently used[10] to produce **1**. In addition, EtOH, EtOAc, CO_2 and H_2O can be obtained from renewable sources (Principle 7). Both strategies avoid the derivatization required in the industrial process, as recommended by Principle 8. Finally, our strategies involve the use of organic solvents in the presence of O_2 which, without due care, could increase the chance of accidents, in contravention of Principle 12, though we mitigate the risk by adding CO_2 or H_2O.

More quantitatively, one can apply a number of metrics,[37,38] albeit only approximately as our strategies are not fully optimized and some of the required data are not available for the existing industrial process. The simplest concept is the E Factor ($kg_{waste}/kg_{product}$) based on the stoichiometry of the reaction, but ignoring water.[39] Although the underlying chemistry is the same, the theoretical E Factors for our strategies is slightly lower than for the commercial process[10] which involves the additional esterification. The actual E factors are all higher because the isolated yield is considerably less than 100%, (see Table 3, entries 1 & 2). We now assess the data on the strategies in terms of two factors, E_1 and E_2. E_1, is defined as the weight of all waste per unit weight of **1;** that is including all reagents, catalysts, and solvents used for the reaction *and* the work up (but excluding water, and O_2). E_2 is the same as E_1 but excluding all of the solvents. In addition for strategy 1, we calculate E_1 with and without including CO_2. All values are summarized in Table 3.

Bearing in mind that all values are necessarily approximate, Table 3 (entries 3-5) indicates that strategy 1 with an assumed 90% recycle of CO_2 has an *unoptimized* value of E_1 similar to that of the industrial process.[10] It has a somewhat higher E_2 value largely because we have assumed a single use of the Amberlyst. By contrast, strategy 2 (entries 6-8) has higher values of E_1 than either the industrial process or strategy 1, largely because of the lower solubility of **1** in aqueous mixtures; E_1 drops, substantially on recycle (see entry 8, and Fig 3A). Of course, solvent could be recycled in any of the processes but the beauty of strategy 2 is that the solvent, acid and photocatalyst can all be recycled directly *without* purification. Obviously, such recycling will be limited by the build-up of side products and could not be carried out indefinitely but the impact of recycling on E_1 is large. E_2 factors for Strategy 2 are substantially lower than for the other processes and the solvent, EtOH, is one of the highest rated in terms of its Renewability Index.[37] Sheldon[40] has suggested that one should introduce and Environmental Quotient, Q to reflect the relative toxicity of the various wastes. In this context, it is particularly important that both strategies eliminate the need for DCM as a solvent and that strategy 2 provides an opportunity to eliminate TFA (entries 6 & 7).

Entry 8 shows that one could reduce the E factors dramatically by increasing the yield of **1** and our strategies do have features which suggest that some increase may be possible

following further optimization, namely the reduction in acid-induced decomposition of **1** **(**either by use of a solid acid resin or by the presence of H_2O), and secondly the observation that even small amounts of THF have a positive effect on yield of **1** Table 2.

Table 3: Comparison of E factors for Strategies 1 & 2 and the commercial process for making **1** (details of the calculations are presented in the ESI)

Entry	Process	Photocatalyst/ Acid Catalyst	Solvent(s)	Yield	E_1 (no water)	E_2 (no solvent)
1	Theoretical[a]	–	–	100%	0 (0.45)[b]	0 (0.45)[b]
2		–	–	50%	0.84	0.84
3	Sanofi[c]	TFA, TPP	DCM, Heptane[d]	55%	36	4.8
4	Strategy 1 (Table 1 entry 3)	Amberlyst/TPP[e]	Toluene/liq CO_2 (4 passes)	39%	23[f] (97)[g] (31)[h]	8
5	Strategy 1 (Table 1, entry 4)	Amberlyst/TPP[e]	Toluene/liq CO_2 (long reactor, single pass)	39%	30[f] (104)[g] (37)[h]	15
6	Strategy 2 (Table S4, entry 15)	H_2SO_4, $Ru(bpy)_3^{2+}$	EtOH/H_2O[i]	38%	210	1.8
7	Strategy 2 (Table S4, entry 15 & Scheme S6)	H_2SO_4, $Ru(bpy)_3^{2+}$	EtOH/H_2O[i] (3 cycles)	37%	101	1.5
8	Strategy 2 (Table 2, entry 2)	TFA, $Ru(bpy)_3^{2+}$	THF/H_2O[j]	(50%)[k]	73	1.3

[a] Based on the stoichiometric equation for **2** → **1**; [b] Numbers in parentheses for the Sanofi process[10] including the waste from the esterification step; [c] see ref 10, for this and other processes, the amount of O_2 has been ignored as insufficient data are available; [d] Requires additional solvents, EtOH and H_2O for purification; [e] Assuming that the Amberlyst TPP is damaged and cannot be used for further reactions; [f] Ignoring the CO_2; [g] including mass of CO_2; [h] Assuming a recycle of CO_2 with a 10% loss in each cycle as found in industrial hydrogenation in $scCO_2$, see Ref 21; [i] EtOH:H_2O 80:20; [j] THF:H_2O 60:40; [k] In this experiment, **1** was obtained in solution with 66% yield but not isolated – therefore 50% isolated yield has been assumed.

Conclusions

The conversion of **3** to **1** is intriguingly complex. We have shown that application of the principles of green chemistry has opened up a wider range of options for carrying out this transformation. Liquid CO_2 offers interesting possibilities, especially in process safety because of the inertness of CO_2 towards oxidation and in the possibility of implementing a continuous process. However, the more immediate impact is likely to come from conventional solvents. The use of aqueous mixtures offers the opportunity for solvent manipulations, particularly in the work up of the product, that are not possible with the solvents currently used in this process. In addition, the reaction can be carried out at near ambient temperatures in the presence of water, thereby eliminating the need for energy demanding refrigeration. Some of the approaches described here hold promise for rapid implementation on a larger scale, thereby taking us a step closer to more affordable artemisinin with benefits not only to malaria sufferers across the world but also to the producers of *Artemisia annua* by giving added value to their crop which, apart from **1**, can additionally yield **2**, the starting material for the semi-synthetic route.

As pointed out over a century ago,[41] photochemistry has great potential for chemical manufacture. However, it is only quite recently that the need for cleaner processes to make complex molecules has reawakened interest in process photochemistry, and the strategies introduced here are applicable to chemistry beyond transforming **2** into **1**. Liquid CO_2 probably has the lowest cost of any solvent obtainable in high purity which is important in

processing pharmaceutical chemicals. Ion exchange resins such as Amberlyst could be used to immobilize a wider range of homogeneous catalysts, in addition to photocatalysts, to generate dual- or multi-functional immobilized catalysts. Our use of aqueous mixtures of common solvents is a timely reminder that mixing solvents can generate a tunability of properties reminiscent of more expensive 'designer' solvents.[42] Finally, we have demonstrated that applying the principles of green chemistry to even well-studied reactions can lead to new and unexpected approaches which have potential processing benefits beyond being greener.

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Additional information

Supplementary Materials
Materials and Methods
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